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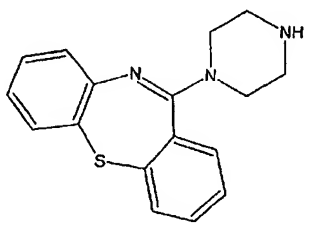
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METABOLITE OF QUETIAPINE



(I)

(57) Abstract: A method of treating anxiety, agitation, hostility, panic, eating disorders, affective symptoms, mood symptoms, negative and positive psychotic symptoms commonly associated with schizophrenia, dementia, anxiety, depression, mood disorders, bipolar disorders, bipolar mania, bipolar depression, cognitive disorders and neurodegenerative disorders comprising administering an effective amount of Formula (I) or its pharmaceutically acceptable salt. In another aspect of the invention a pharmaceutical composition is provided comprising an effective amount of Formula (I) or its pharmaceutically acceptable salt and at least on pharmaceutically acceptable carrier or diluent.

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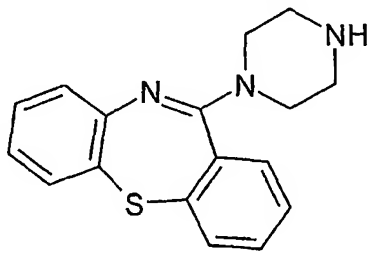
METABOLITE OF QUETIAPINE

BACKGROUND OF THE INVENTION

The goal of antipsychotic drug development has been to develop agents with increased efficacy and safety along with fewer of the side effects commonly associated with the older antipsychotic medications. Quetiapine fumarate is described in U.S. Patent Number 4,879,288, which is incorporated herein by reference. Quetiapine fumarate is able to treat both the positive (hallucinations, delusions) and negative symptoms (emotional withdrawal, apathy) of psychosis and is associated with fewer neurological and endocrine related side effects compared to older agents. Quetiapine fumarate has also been associated with a reduction in hostility and aggression. Quetiapine fumarate is associated with fewer side effects such as EPS, acute dystonia, acute dyskinesia, as well as tardive dyskinesia. Quetiapine fumarate has also helped to, enhance patient compliance with treatment, ability to function and overall quality of life, while reducing recidivism. P. Weiden et al., *Atypical antipsychotic drugs and long-term outcome in schizophrenia,* 11 J. Clin. Psychiatry, 53-60, 57 (1996). Because of quetiapine fumarate's enhanced tolerability profile its use is particularly advantageous in the treatment of patients that are hypersensitive to the adverse effects of antipsychotic (such as elderly patients). Metabolites of quetiapine fumarate have been identified, E. Warawa et al. *Behavioral approach to nondyskinetic dopamine antagonists: identification of Seroquel,* 44 J. Med. Chem., 372 -389 (2001) and U.S. 4,879,288. One compound described in U.S. 4,879,288 is 11-piperazin-1-yldibenzo[*b,f*][1,4]thiazepine which has now been identified as a metabolite of quetiapine fumarate.

SUMMARY OF THE INVENTION

11-piperazin-1-yldibenzo[*b,f*][1,4]thiazepine has the structure as shown by Formula I:



I

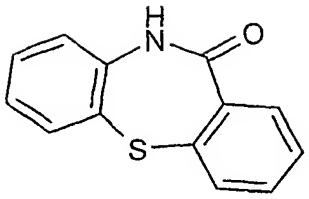
Provided herein is a method of treating at least one symptom or condition associated with schizophrenia, dementia, anxiety, depression, mood disorders, bipolar disorders, bipolar mania, bipolar depression, cognitive disorders, psychosis and neurodegenerative disorders comprising administering to a mammal an effective amount of the compound of Formula I or its pharmaceutically acceptable salt. In another aspect of the invention provided is a pharmaceutical composition comprising an effective amount of the compound of Formula I or its pharmaceutically acceptable salt and at least one pharmaceutically acceptable carrier. Also provided is a method of treating the symptoms or condition provided herein comprising administering to a mammal an effective amount of the above-mentioned pharmaceutical composition. Also provided is the use of the compound of Formula I and/or the above-mentioned pharmaceutical composition in the treatment of the symptoms or conditions provided herein in mammals. Also provided is the use of the compound of Formula I administered in combination with one or more other therapeutically active agents. Further, provided herein is the use of the compound of Formula I and/or the pharmaceutical composition in the manufacture of a medicament for use in the treatment of the symptoms or conditions provided herein in mammals.

DETAILED DESCRIPTION OF THE INVENTION

The compound of Formula I is a dibenzothiazepine that has shown antidopaminergic activity. It has been shown to interact with a broad range of neurotransmitter receptors but has a higher affinity for serotonin (5-HT_2) receptors relative to dopamine (D_2) receptors in the brain. The compound of Formula I may be used as an antipsychotic with a reduction in the potential to cause side effects such as acute dystonia, acute dyskinesia, as well as tardive dyskinesia. Further the compound of Formula I may be used to treat patients of all ages and is advantageous in the treatment of elderly patients.

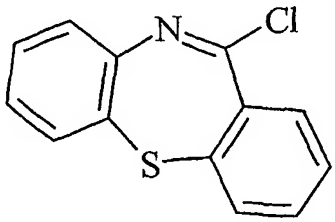
The term "mammal" means a warm-blooded animal, preferably a human.

The compound of Formula I may be made by a variety of methods known in the chemical arts. The compound of Formula I may be prepared by starting from known compounds or readily prepared intermediates including taking the lactam of Formula II:



II

which may be prepared by methods well known in the literature, for example, as described by J. Schmutz et al. Helv. Chim. Acta., 48:336 (1965). The lactam of Formula II is treated with phosphorus chloride to generate the immino chloride of Formula III:



III

The immino chloride of Formula III may also be generated with other agents such as thionyl chloride or phosphorous pentachloride. The immino chloride is then reacted with piperazine to give the compound of Formula I.

The compound of Formula I provided herein is useful as a free base, but may also be provided in the form of a pharmaceutically acceptable salt, and/or in the form of a pharmaceutically acceptable hydrate. For example, pharmaceutically acceptable salts of Formula I include those derived from mineral acids such as for example: hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydroiodic acid, nitrous acid, and phosphorous acid. pharmaceutically acceptable salts may also be developed with organic acids including aliphatic mono dicarboxylates and aromatic acids. Other pharmaceutically acceptable salts of Formula I include but are not limited to hydrochloride, sulfate, pyrosulfate, bisulfate, bisulfite, nitrate, and phosphate.

A clinician may determine the effective amount by using numerous methods already known in the art, an example of which is the BPRS cluster score that can be used to assess levels of hostility and positive symptoms. The term "treating" within the context of the present invention encompasses to administer an effective amount of the compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a

recurring symptom or condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

Particularly, the symptoms and conditions that may be treated by the administration of Formula I or its pharmaceutically acceptable salt or a pharmaceutical composition of Formula I, include but are not limited to anxiety, agitation, hostility, panic, eating disorders, affective symptoms, mood symptoms, negative and positive psychotic symptoms commonly associated with psychosis and neurodegenerative disorders.

Particular amount of the compound of Formula I or its pharmaceutically acceptable salt that may be administered in an amount up to 750 mg per day; the amount of the compound of Formula I or its pharmaceutically acceptable salt may be administered between 1 mg and 600 mg per day.

The compound of Formula I may be administered comprising a predetermined dosage of the compound of Formula I to a mammal between one and four times a day, wherein the predetermined dosage is between 1 mg and 600 mg.

The present invention also provides a method of treating the symptoms or conditions provided herein comprising the step of administering an initial predetermined dosage of a compound of Formula I to a human patient twice a day, wherein the predetermined dosage is between 1 mg and 30 mg with increases in increments of 1-50 mg twice daily on the second and third day as tolerated. Thereafter, further dosage adjustments can be made at intervals of no less than 2 days.

In one embodiment of the invention the pharmaceutical composition comprises up to 750 mg of the compound of Formula I or its pharmaceutically acceptable salt thereof per day.

In another embodiment of the invention, the pharmaceutical composition may comprise between 100 mg and 400 mg per day of the compound of Formula I or a pharmaceutically acceptable salt thereof.

The pharmaceutical composition of the invention may accordingly be obtained by conventional procedures using conventional pharmaceutical excipients. Thus, pharmaceutical compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

For preparing pharmaceutical compositions from the compound of Formula I of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form

preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

The composition of the invention may be administered by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. The size of the dose for therapeutic or prophylactic purposes of a compound of the FormulaI will naturally vary according to the nature and severity of the symptoms or conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

Another aspect of the invention provides a compound of Formula I, or its pharmaceutically acceptable salt or solvate thereof, for use in treating the symptoms or conditions provided herein.

In a further aspect, the present invention provides the use of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in treating the symptoms or conditions provided herein.

In a further aspect, the present invention relates to methods of treating at least one symptom or condition associated with schizophrenia, dementia, anxiety, depression, mood disorders, bipolar disorders, bipolar mania, bipolar depression, cognitive disorders, psychosis and neurodegenerative disorders comprising administering to a mammal an effective amount of the compound of Formula I or its pharmaceutically acceptable salt and one or more of other therapeutically active agents, benzodiazepines, 5-HT_{1A} ligands, 5-HT_{1B} ligands, 5-HT_{1D} ligands, mGluR2A agonists, mGluR5 antagonists, antipsychotics, NK1 receptor antagonists, antidepressants, or serotonin reuptake inhibitors administered in combination as part of the same pharmaceutical composition, as well as to methods in which such active agents are administered separately as part of an appropriate dose regimen designed to obtain the benefits of combination therapy. The appropriate dose regimen, the amount of each dose of an active agent administered, and the specific intervals between doses of each active agent will depend upon the subject being treated, the specific active agent being administered and the nature and severity of the specific disorder or condition being treated. In general, the compounds of this

invention, when used as either a single active agent or when used in combination with another active agent, will be administered to a subject in an amount up to about 750 mg per day, in single or divided doses. Such compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day. Variations may nevertheless occur depending upon the subject being treated and the individual response to the treatment, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases larger doses may be employed to achieve the desired effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

Exemplary benzodiazepines may include but are not limited to adinazolam, alprazolam, bromazepam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, balezepam, lorazepam, midazolam, nitrazepam, oxazepam, quazepam, temazepam, triazolam and equivalents thereof.

Exemplary 5-HT_{1A} and/or $5HT_{1B}$ ligands may include but are not limited to buspirone, alnespirone, elzasonan, ipsapirone, gepirone, zopiclone and equivalents thereof.

Exemplary mGluR 2 agonists may include (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid, (2S,3S,4S)alpha-(carboxycyclopropyl)glycine, and 3,5-dihydroxyphenylglycine.

Exemplary antidepressants may include but are not limited to maprotiline, amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortryptyline, protriptyline, trimipramine, SSRIs and SNRIs such as fluoxetine, paroxetine, citalopram, escitalopram, sertraline, venlafaxine, fluoxamine, and reboxetine.

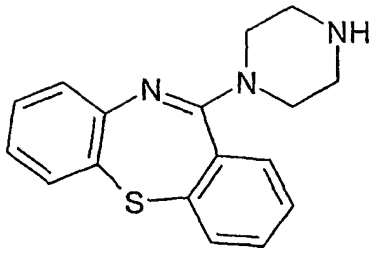
Exemplary antipsychotics may include but are not limited to clozapine, risperidone, quetiapine, olanzapine, amisulpride, sulpiride, zotepine, chlorpromazine, haloperidol, ziprasidone, and sertindole.

The following examples provided are not meant to limit the invention in any manner and are intended for illustrative purposes only.

EXAMPLES

Example 1

Preparation of 11-piperazin-1-yldibenzo[*b*,*f*][1,4]thiazepine



Into a 1000ml round-bottom flask equipped with a magnetic stirring bar and reflux condenser with a nitrogen inlet was charged with 25.0 grams (g) (0.110 mole) of dibenzo[b,f][1,4]thiazepine-11(10-H)-one (made by the method disclosed by J. Schmutz et al. Helv. Chim. Acta., 48: 336 (1965)), as a dry solid, followed by 310ml $POCl_3$ and 3ml of N,N-dimethylaniline. The reaction mixture was heated at reflux (106 degrees C) for 6 hours giving a clear orange solution. The reaction was then cooled to room temperature, and $POCl_3$ removed on the rotary evaporator leaving an orange oil. This residue was partitioned between ice –water (500ml) and Ethyl acetate (800ml). The layers were separated and the aqueous phase extracted with Ethyl acetate (3 X 200ml). The combined Ethyl acetate extracts were dried over $MgSO_4$, filtered, and then stripped down on the rotary evaporator, leaving the crude Imino chloride as a light yellow solid (26.26g, 97% yield). The structure was confirmed by NMR and Mass Spectrum (300MHz, $CDCl_3$; ES+, M+1 = 246.7). Crude Imino chloride (27.35g, 0.111 mole) was added to 1000ml o-xylene in a 2000ml round-bottom flask equipped with a magnetic stir bar and a reflux condenser with nitrogen inlet. To this solution was added commercially available piperazine (47.95g, 0.557 mole) in one portion as a dry solid at room temperature. The mixture was stirred until nearly all the piperazine dissolved. Then the reaction mixture was heated at reflux (142 degrees C) for 40 hours (out of convenience). The reaction was then allowed to cool to room temperature, and an aliquot was partitioned between 1N NaOH / CH_2Cl_2. The organic phase was checked by TLC (silica gel, CH_2Cl_2 / Methanol 90:10, Iodoplatinate visualized) and showed clean conversion to one major product (Rf = 0.45). A drop of the reaction solution was diluted with CH_3CN to prepare a sample for LC / MS analysis, which confirmed the presence of the desired product (M+1 = 296.4). The reaction mixture was stripped down on the rotary evaporator under high vacuum to remove the xylene. The residue was partitioned between 1N NaOH (400ml) and CH_2Cl_2 (200ml). The layers were separated, and the aqueous phase further extracted with CH_2Cl_2 (3 X 200ml). The combined CH_2Cl_2 extracts were washed with brine (200ml), then

dried over $MgSO_4$, filtered, and stripped down on the rotary evaporator to give the crude title compound as a yellow gum (35.3g). The crude free base was purified by flash column chromatography over silica gel (600g) eluting with a gradient of 0 to 20% Methanol in CH_2Cl_2. Fractions containing the pure desired product were combined and stripped down on the rotary evaporator, to afford the purified free base as a light yellow foam (25.67g, 78% yield).

Example 2

Preparation of 11-piperazin-1-yldibenzo[*b*,*f*][1,4]thiazepine, dihydrochloride salt

The free base was converted to it's dihydrochloride salt by dissolving it in a mixture of Methanol (125ml) and Diethyl ether (125ml), then treating with 250ml of 1.0 M HCl/ Ether (Aldrich). An off -white gummy solid separated initially, and the mixture was further diluted with 500ml ether. The gummy solid did not solidify on prolonged stirring. The solvents were decanted away from the gum. The gum was treated with absolute Ethanol (200ml), then stirred until crystallization occurred, giving a thick white suspension of crystals. This mixture was then slowly diluted with ether (800ml) and allowed to stir overnight to complete the crystallization. The dihydrochloride salt was isolated by filtration, washed with ether (3 X 50ml), then dried in vacuum at 60 degrees C to afford the dihydrochloride salt of the title compound as a white solid (31.64g, 98.8% conversion).

ANALYSIS:

The product was characterized by NMR and LC / MS (300MHz, $CDCl_3$; AP+, M+1 = 296.4).

Example 3 (mice assays)

An assessment of dopamine antagonism was made in rodent models. The methods and procedures used can be found in *J. Med. Chem.*, 44 (3), 372 -389, 2001 and are incorporated herein by reference. The results are as follows the binding affinity for brain serotonin 5-HT_2 receptor was 27 K1 nM, and for dopamine D_1 and D_2 receptors was 1489 and 234 K1 nM, respectively. These results show that the compound of the present invention as the dihydrochloride salt interacts with a broad range of neurotransmitter receptors, however, the assay also reveals that that the compound of the present invention as the dihydrochloride salt has a higher affinity for serotonin (5-HT_2) receptors relative to dopamine (D_2) receptors in the brain. It is this combination of serotonin and dopamine receptor antagonism, with higher relative 5-HT_2 to D_2 receptor affinity that indicates the compound of Formula I as a potent

atypical antipsychotic. J. Goldstein, *Quetiapine Fumarate (Seroquel): a new atypical antipsychotic,* 35(3) Drugs of Today 193-210 (1999).

What is claimed is:

1. A method of treating at least one symptom or condition associated with schizophrenia, dementia, anxiety, depression, mood disorders, bipolar disorders, bipolar mania, bipolar depression, cognitive disorders, psychosis, and neurodegenerative disorders, comprising administering to a mammal an effective amount of the compound having the formula 11-piperazin-1-yldibenzo[*b*,*f*][1,4]thiazepine or its pharmaceutically acceptable salt.

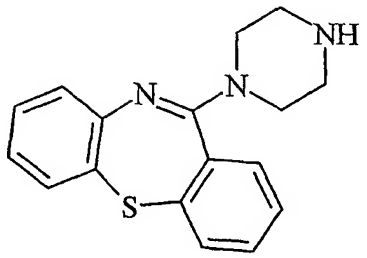
2. The method as recited in Claim 1 wherein the symptoms or condition comprises anxiety, agitation, hostility, panic, eating disorders, affective symptoms, mood symptoms, negative and positive psychotic symptoms.

3. The method as recited in Claim 1 wherein the pharmaceutically acceptable salt is a dihydrochloride salt.

4. A method of treating at least one symptom or condition associated with schizophrenia, dementia, anxiety, depression, mood disorders, bipolar disorders, bipolar mania, bipolar depression, cognitive disorders, psychosis, and neurodegenerative disorders, comprising administering an effective amount of a first component of 11-piperazin-1-yldibenzo[*b*,*f*][1,4]thiazepine or its pharmaceutically acceptable salt, in combination with an effective amount of a second component selected from one or more other therapeutically active agents, benzodiazepines, 5-HT_{1A} ligands, 5-HT_{1B} ligands, 5-HT_{1D} ligands, mGluR2A agonists, mGluR5 antagonists, antipsychotics, NK1 receptor antagonists, antidepressants, or serotonin reuptake inhibitors.

5. Use of 11-piperazin-1-yldibenzo[*b*,*f*][1,4]thiazepine or its pharmaceutically acceptable salt in the treatment of schizophrenia, dementia, anxiety, depression, mood disorders, bipolar disorders, bipolar mania, bipolar depression, cognitive disorders, psychosis, neurodegenerative disorders, anxiety, agitation, hostility, panic, eating disorders, affective symptoms, mood symptoms, negative and positive psychotic symptoms comprising administering to a mammal an effective amount of 11-piperazin-1-yldibenzo[*b*,*f*][1,4]thiazepine or its pharmaceutically acceptable salt.

6. A pharmaceutical composition comprising an effective amount of the compound of Formula I



I

or its pharmaceutically acceptable salt together with at least one pharmaceutically acceptable carrier or diluent.

7. The composition as recited in Claim 5 wherein the pharmaceutically acceptable salt is a dihydrochloride salt.

8. A method of treating at least one symptom or condition associated with schizophrenia, dementia, anxiety, depression, mood disorders, bipolar disorders, bipolar mania, bipolar depression, cognitive disorders, psychosis, neurodegenerative disorders comprising administering to a mammal an effective amount of the pharmaceutical composition of claim 5.

9. The method as recited in Claim 7 wherein the symptoms or condition comprises anxiety, agitation, hostility, panic, eating disorders, affective symptoms, mood symptoms, negative and positive psychotic symptoms.

10. Use of the pharmaceutical composition of claim 5 in the manufacture of a medicament for the treatment of schizophrenia, dementia, anxiety, depression, mood disorders, bipolar disorders, bipolar mania, bipolar depression, cognitive disorders, psychosis, neurodegenerative disorders, anxiety, agitation, hostility, panic, eating disorders, affective symptoms, mood symptoms, negative and positive psychotic symptoms in mammals.

11. Use of 11-piperazin-1-yldibenzo[*b*,*f*][1,4]thiazepine in the manufacture of a medicament for the treatment of schizophrenia, dementia, anxiety, depression, mood disorders, bipolar disorders, bipolar mania, bipolar depression, cognitive disorders, psychosis, neurodegenerative disorders, anxiety, agitation, hostility, panic, eating disorders, affective symptoms, mood symptoms, negative and positive psychotic symptoms in mammals.

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/GB2004/002783

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/554 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 546 226 A (HUNZIKER FRITZ ET AL) 8 December 1970 (1970-12-08) column 8, line 4-10	1-11
A	DEVANE C LINDSAY ET AL: "Clinical pharmacokinetics of quetiapine: An atypical antipsychotic" CLINICAL PHARMACOKINETICS, vol. 40, no. 7, 2001, pages 509-522, XP009037259 ISSN: 0312-5963 figure 1	1-11
A	MUTSCHLER E: "Arzneimittelwirkungen" 1991, WISSENSCHAFTLICHE VERLAGSGESELLSCHAFT , STUTTGART , XP002298363 page 127, paragraph entitled "Indikationen"	1-5,8-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 September 2004	19/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Borst, M

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/GB2004/002783

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy:Although claims 1-5, 8, 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ormation on patent family members

I nal Application No
PCT/GB2004/002783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3546226 A	08-12-1970	CH 481133 A	15-11-1969
		CH 484924 A	31-01-1970
		CH 436297 A	31-05-1967
		CH 450422 A	31-01-1968
		US 3158623 A	24-11-1964
		AT 292716 B	15-08-1971
		AT 292717 B	15-08-1971
		AT 292718 B	15-08-1971
		AT 292707 B	10-09-1971
		BE 712114 A	13-09-1968
		CH 517759 A	15-01-1972
		CH 514612 A	31-10-1971
		CH 499539 A	30-11-1970
		DE 1720007 A1	19-05-1971
		ES 351389 A1	01-12-1969
		FR 8046 M	10-08-1970
		GB 1216523 A	23-12-1970
		IL 29571 A	27-04-1972
		NL 6406089 A	01-12-1964
		NL 6803570 A	16-09-1968
		NO 123459 B	22-11-1971
		SE 364277 B	18-02-1974
		US 3852446 A	03-12-1974
		US 3683034 A	08-08-1972
		CH 481940 A	30-11-1969
		CH 481941 A	30-11-1969
		CH 481942 A	30-11-1969
		US 3539573 A	10-11-1970
		US 3751415 A	07-08-1973
		US 3758479 A	11-09-1973
		US 3793325 A	19-02-1974
		US 3908010 A	23-09-1975
		CH 484937 A	31-01-1970
		CH 484926 A	31-01-1970
		CH 484927 A	31-01-1970
		CH 484928 A	31-01-1970
		AT 258912 B	27-12-1967
		AT 250975 B	12-12-1966
		AT 252925 B	10-03-1967
		BE 648683 A	01-12-1964
		CH 450424 A	31-01-1968
		CH 450425 A	31-01-1968
		CH 450426 A	31-01-1968
		DE 1470426 A1	18-12-1969
		DK 107481 C	05-06-1967
		DK 107482 C	05-06-1967
		DK 118463 B	24-08-1970
		DK 107552 C	12-06-1967
		FI 42214 B	02-03-1970
		FR 3485 M	